

Two of the cell lines, DSL 6/A (pancreatic) and Dunning R3327-H (prostate) which are rich in somatostatin (SST-2) receptors indicated slow perfusion of the agent into the tumor over time. Images were taken at 2 minutes and 30 minutes post administration of ICG. Reasonable images were obtained for each. The third line, CA20948 (pancreatic), indicated only a slight and transient perfusion that was cleared after only 30 minutes post injection. This indicated that there was no non-specific localization of ICG into this tumor line compared to the other two lines which suggested a vastly different vascular architecture for this type of tumor (Figure 2). The first two tumor lines (DSL 6/A and R3327-H) were not as highly vascularized as CA20948 which is also rich in somatostatin (SST-2) receptors. Consequently, the detection and retention of a dye in the CA20948 tumor model is an important index of receptor-mediated specificity.

Example 10

Imaging of Rat Pancreatic Acinar Carcinoma (CA20948) With Cytate 1

The peptide, octreotate, is known to target somatostatin (SST-2) receptors. Therefore, the cyano-octreotates conjugate, Cytate 1, was prepared as described in Example 4. The pancreatic acinar carcinoma, CA20948, was induced into male Lewis rats as described in Example 9.

The animals were anesthetized with xylazine: ketamine: acepromazine (1.5: 1.5: 0.5^{v/v}) at 0.8 ml/kg via intramuscular injection. The left flank was shaved to expose the tumor and surrounding surface area. A 21-gauge butterfly needle equipped with a stopcock connected to two syringes containing heparinized saline was placed into the tail vein of the rat. Patency of the vein was checked prior to administration of Cytate 1 via the butterfly

apparatus. Each animal was administered a 0.5 ml dose of a 1.0 mg/ml solution of Cytate 1 in 25%^(v/v) dimethylsulfoxide/ water.

Using the CCD camera apparatus, dye localization in the tumor was observed. Usually, an image of the animal was taken pre-injection of contrast agent, and the pre-injection image was subsequently subtracted (pixel by pixel) from the post-injection images to remove background. However, the background subtraction was not done if the animal had been removed from the sample area and was later returned for imaging several hours post injection. These images demonstrated the specificity of cytate 1 for the SST-2 receptors present in the CA20948 rat tumor model.

At one minute post administration of cytate 1 the fluorescent image suggested the presence of the tumor in the left flank of the animal (Figure 3a). At 45 minutes post administration, the image showed green and yellow areas in the left and right flanks and in the tail, however, there was a dark blue/blue green area in the left flank (Figure 3b). AT 27 hours post administration of the conjugate, only the left flank showed a blue/blue green fluorescent area (Figure 4).

Individual organs were removed from the CA20948 rat which was injected with cytate 1 and were imaged. High uptake of the conjugate was observed in the pancreas, adrenal glands and tumor tissue. Significant lower uptake was observed in heart, muscle, spleen and liver (Figure 5). These results correlated with results obtained using radiolabeled octreotate in the same rat model system (M. de Jong, et al. *Cancer Res.* 1998, 58, 437-441).

Example 11

Imaging of Rat Pancreatic Acinar Carcinoma (AR42-J) with Bombesinate

The AR42-J cell line is derived from exocrine rat pancreatic acinar carcinoma. It can be grown in continuous culture or maintained *in vivo* in athymic nude mice, SCID mice, or in Lewis rats. This cell line is particularly attractive for *in vitro* receptor assays, as it is known to express a variety of hormone receptors including cholecystokinin (CCK), epidermal growth factor (EGF), pituitary adenylate cyclase activating peptide (PACAP), somatostatin (sst₂) and bombesin.

In this model, male Lewis rats were implanted with solid tumor material of the AR42-J cell line in a manner similar to that described in Example 9. Palpable masses were present 7 days post implant, and imaging studies were conducted on animals when the mass had achieved approximately 2 to 2.5 g (10-12 days post implant).

Figure 6 shows the image obtained with this tumor model at 22 hours post injection of bombesinate. Uptake of bombesinate was similar to that described in Example 10 for uptake of cytate 1 with specific localization of the bioconjugate in the tumor.

Example 12

Imaging of Rat Pancreatic Acinar Carcinoma (CA20948) with Cytate 1 by Fluorescence Endoscopy

Fluorescence endoscopy is suitable for tumors or other pathologic conditions of any cavity of the body. It is very sensitive and is used to detect small cancerous tissues, especially in the lungs and gastrointestinal (GI) system. Methods and procedures for fluorescence endoscopy are well-documented [Tajiri H., et al. Fluorescent diagnosis of experimental gastric